UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,822	04/24/2001	Thorvald Eelco Wallaart	702-010272	3747

7590 09/30/2005

Barbara E Johnson
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219-1818

EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,822	WALLAART ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43,45-65 and 75-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43,45,47-65 and 75-86* is/are rejected.

7)☒ Claim(s) *46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____:

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDD

FINAL REJECTION

1. Applicants' petition under 37 CFR 1. 137(b), filed July 13, 2005, to revive the above-identified application was considered by the Office of Petitions and GRANTED.

2. Applicants' Amendment filed July 13, 2005, is acknowledged. Applicant's arguments filed July 13, 2005 have been considered and not found to be persuasive. The reasons are discussed following the rejection(s).

3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant' s response and withdrawn.

4. Claims withdrawn :

Claims 66, 71-74 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed. Claims 44, 66-68 & 70 have been canceled.

5. Claims 43, 45-65 and 75-86 are under consideration in this examination.

6. **Rejoinder:** The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the

rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See " Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

As indicated in the rejoinder notice above it is emphasized that until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Therefore, the previously withdrawn claims remain withdrawn, as the product claims are so far not found to be allowable.

7. Claims 85-86 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims dependent upon canceled claim 44. Applicants are required to place the claims in proper dependent form to overcome this rejection.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64-65 recites the limitation "host cells" in claim 50. There is insufficient antecedent basis for this limitation in the claim. Claims 64-65 are rejected for lack of antecedent basis.

9. ***35 USC 101-non-statutory subject matter***

35 U.S.C. §101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 50-63 & 75-84 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter.

Claims 50-63 & 75-84, as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified" as taught by page [insert page number] of specification. See MPEP 2105.

10. ***35 U.S.C.§ 112, first paragraph (Enablement)***

Claims 43, 45, 47-65 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA sequence of SEQ ID NO: 13 encoding an amorpha-4,11-diene synthase of SEQ

ID NO: 14, does not reasonably provide enablement for a DNA sequence that is 70%, 80%, 90% or 95% (claims 43, 45 & 85-86) identical to SEQ ID NO : 13 and encodes a protein having amorpha-4,11-diene synthase activity or any host tissue or organism transformed with such a DNA.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))[*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are [the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The specification provides guidance and examples for making an isolated DNA sequence comprising SEQ ID NO: 13 and the encoded polypeptide sequence of SEQ ID NO: 14 [amorpha-4,11-diene synthase]. However, the specification does not teach the specific structural/catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered. The state of the art as exemplified by Attwood et al. [Comput. Chem. 2001, col. 54(4), pp. 329-39] is such that " ..we do not fully understand the rules of protein folding, so we cannot predict protein structure; and we cannot invariably diagnose protein function, given the knowledge only of its sequence or structure

in isolation" (see abstract and the entire publication). Further Ponting [Brief. Bioinform. March 2001, Vol. 2(1), pp. 19-29] states that " ···predicting function by homology is a qualitative, rather than quantitative process and requires particular care to be taken, due attention should be paid to all available clues to function, including orthologue identification, conservation of particular residue types, and the co-occurrence of domain in proteins" (see abstract and the entire publication).

The standard of meeting enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed polynucleotide is enormous and entails selecting specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make a claimed polynucleotide and determining by assays whether the polypeptide has activity. The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for enzyme structure/function which must be preserved. Thus, searching for the specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make polynucleotide that is at least 70%, 80%, 90% or 95% identical to a polynucleotide comprising nucleotide sequence of SEQ ID NO: 13 is well outside the realm of routine experimentation and predictability in the art of success in determining whether the resulting polypeptide has activity (same, other or none) is extremely low since no structural motifs essential for enzyme structure and activity/function which must be preserved. Similarly transforming any tissue or organism which may be human tissue or a human is neither exemplified nor enabled. Claims drawn to transgenic tissue or organism (claims 64-65)

containing at least a part of host cell consisting of SEQ ID NO: 13 is also not enabled for the foregoing reasons.

Applicants' attention is specially drawn to Accession No. AF327526 [Liu et al, 2001, not prior art], a DNA sequence encoding sesquiterpene cyclase [CN : Farnesyl pyrophosphate cyclase] and is 98.6% identical to Applicants' SEQ ID NO: 13. [see the enclosed sequence search alignment]. As can be seen, a difference of 0.4% between Accession No. AF327526 and Applicants' SEQ ID NO: 13, results in the DNA encoding a totally different protein having different enzyme activity. Therefore, modifying a DNA sequence encoding amorpha-4,11-diene synthase by 5-30% will be highly unpredictable, and based upon the works of Liu et al., most likely will not produce a DNA capable of encoding a protein having amorpha-4,11-diene synthase activity.

Further, the specification does not support the broad scope of the claims which further encompass transgenic tissues or microorganisms comprising such DNA sequences encoding amorpha-4,11-diene synthase from any source or expression of parts of host cells (claims 64 & 65) and/or transformed tissue or organism which may be a human tissue or human, because the specification only teaches a single DNA species capable of encoding amorpha-4,11-diene synthase from *Artimisia*. The prior art is silent about DNA from other plants, microorganisms, etc., which are capable of encoding amorpha-4,11-diene synthase.

Therefore, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific catalytic amino acids and structural motifs essential for activity/function which must be preserved and/or other DNA sequences encoding amorpha-4,11-diene synthase, apart from disclosure to transforming any tissue to organism including a human

or a human tissue in order to enable a skilled artisan by providing guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and which of the human tissue or human are capable of being transformed by a plant gene, and detailed knowledge of the ways in which the proteins' structure relates to its function. Without such a guidance, the experimentation left to those skilled in the art is undue.

Applicants' Previous Arguments:

Applicants argue that there is sufficient guidance in the specification, example 2-3, teaching isolation and characterization of the gene encoding amorpha-4,11-diene synthase, total isolation of RNA, the synthesis of cDNA and the construction of cDNA library and farnesyl pyrophosphate (FPP) assay. Applicants submit that the FPP assay described in the examples more than adequately enables one skilled in the art to isolate DNA sequence that are 70% homologous to SEQ ID NO: 13 without undue experimentation and without the need for further teachings related to specific structural motifs necessary for unaltered protein activity/function.

Applicants' arguments have been considered and found not relevant because the points raised by the Applicants do not teach or enable a skilled artisan to modify a protein by 30%.

Further, Applicants have not responded to arguments pertaining to Accession No. AF327526 [Liu et al, 2001, not prior art], wherein a DNA sequence encoding sesquiterpene cyclase [CN : Farnesyl pyrophosphate cyclase] was found to be 98.6% identical to Applicants' SEQ ID NO: 13. [sequence search alignment, previously provided]. Therefore, a 0.4% change in

the sequence identity resulted in the DNA encoding a functionally distinct protein. The rejection is therefore maintained.

New Arguments:

Applicants argue that it is a standard practice in the art to generate homologous fragments of known nucleic acid sequences and to routinely test the protein translated therefrom for a particular activity, and thus is not undue experimentation.

Applicants' argument is considered but not found to be persuasive because the instant specification still do not teach or enable a skilled artisan to modify DNA of SEQ ID NO: 13 by 30% and still be able to encode and active amorpha-4,11-diene synthase. Merely, assaying the activity by standard assay is not sufficient as explained in the following paragraph.

The specification does not support the broad scope of the claims which encompass all modifications of any DNA sequences encoding amorpha-4,11-diene synthase wherein the DNA sequence would have at least 70%, 80%, 90% or 95% to the DNA of SEQ ID NOS: 13, because the specification does **not** establish: (A) regions of the encoded protein or amorpha-4,11-diene synthase structure which may be modified without effecting amorpha-4,11-diene synthase activity; (B) the general tolerance of amorpha-4,11-diene synthase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any phospholipase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. The rejection is therefore maintained.

11. Claims 85-86 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 85-86 depend upon canceled claim 44. Placing the claims in proper dependent form, for example, will overcome this objection.

12. Claim 46 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. **New Matter added to claims only** - [New Matter rejection]

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), **at the time the application was filed**, had possession of the claimed invention. Applicant's addition [new matter] of 'non-human' in claims 75-84, either directly or in a dependent manner, is not supported by the original disclosure. Applicants are required to cancel the new matter in reply to this office action.

The recitation of " non-human,," in Claim 75 (upon which Claims 76-84 depend) does not have support in the specification as filed. Explicit support is required, not inherent support as argued by the Applicants on page 8, 2nd paragraph, of their response.

14. Claims drawn to Specific SEQ ID NO:, without the homology language, free of language such as ' transgenic tissue or organism' , will be in a better condition for allowance. Substituting ' transgenic tissue or organism' with ' transgenic plant tissue or transgenic plant' is suggested as an alternate language.

15. Status of the claims:

Claims 43, 45-65 and 75-86 are pending.

Claim 46 is objected.

Claims 43, 45, 47-65 and 75-86 are rejected.

No claim is allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner' s supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Tekchand Saidha
Primary Examiner, Art Unit 1652
Recombinant Enzymes, E03A61 Remsen Bld.
400 Dulany Street, Alexandria, VA 22314
Telephone : (571) 272-0940
September 26, 2005